REMARKS

I. The Subject Matter of the Claims

The subject matter of the claims relates, in general, to methods of modulating the transport of leptin across the blood-brain barrier.

II. Patentability Argument

A. The Rejection of Claims 1-5 Under 35 U.S.C. §112, First Paragraph, Enablement Should Properly Be Withdrawn

The Examiner contends that claims 1-5 are not enabled because Applicant has assertedly not enabled transport of leptin across the blood-brain barrier (BBB) using all the compounds recited in the claims, by every route of administration in the claims, and with co-administration of other leptin compounds. Applicant respectfully disagrees.

With respect to the compounds used in the method of the invention, Applicant has enabled use of at least one member of each class of compounds recited in the claims. Applicant is not required to demonstrate efficacy of every member of a certain class of compounds, but enable the class such that one of ordinary skill in the art could make and use the invention. Atlas Powder Co. v EI du Pont de Nemours & Co., 750F2d 1569, 224 USPQ 409. Applicant has taught how to measure leptin transport across the BBB (see, for example, Example 1, beginning on page 17, and Example 4, beginning on page 22) in the presence and absence of compounds of each class recited in the claims (e.g., adrenergic agonists, adrenergic antagonists, neurotransmitters, cytokines, amino acids, opiate peptides, purinergic agonists, glutaminergic agonists) that are effective at mediating this transport. Moreover, the claims have been amended to positively recite that said administering is effective to modulate the transport of leptin across the blood brain barrier, when such compositions are administered in combination with leptin.

Applicant notes that the combined administration may be such that the leptin is administered before, after or concurrently with the second agent.

The Examiner specifically points out that certain members of each class do enhance leptin transport, while some members of the class do not enhance leptin transport, as disclosed by Applicant, and provides examples for each class of compounds claimed by Applicant. Applicant submits that, as admitted by the Examiner, the specification enables a working member of each class of compounds recited in the claims, and typically, the specification provides more examples of compounds that do modulate transport than those that do not. The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived would be operative with expenditure of no more effort than is normally required in the art. MPEP 2164.08 citing Atlas Powder Co., *supra*. Experimentation, even if extensive, is not necessarily undue if it is routine in the art. In re Wands, 858 F.2d 731 (Fed. Cir. 1988)).

Moreover, the specification provides multiple examples of methods for determining if a compound modulates leptin transport (see for example, Example 1, beginning on page 17, and Example 4, beginning on page 22). Applicant submits that such experimentation is routine to one of ordinary skill in the art. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim then the enablement requirement is satisfied. In re Fischer, 427 F2d 833, 166 USPQ 18 (CCPA 1970).

Because the specification provides multiple examples of compounds that modulate leptin transport and describes methods for determining if the compound modulates leptin

transport, the specification teaches a worker of skill in the art to determine if a compound in question mediates leptin transport without undue burden, and the scope of the claims as amended is enabled.

Similarly, Applicant has described methods for administering compounds useful in the method of the invention by many different routes, e.g. intravenously, intraperitoneally, intracerebrovascularly, nasally or orally, that are commonly used in the art. For example, page 4, lines 27-30, of the specification describes methods of administration commonly used in the art, Examples 1 and 4 describe intraperitoneal and intravenous administration, Example 6, beginning on page 24, describes intracerebrovascular injection in mice, and page 12, lines 12-23, further describes that the compound to be administered may be modified to enhance its uptake by the various routes of administration.

Because the specification provides multiple examples of routes of administration of compounds in the methods of the invention, all of which are commonly known in the art, and describes methods for determining if the compound modulates leptin transport,(see Example 1 and 4) the specification teaches a worker of skill in the art to use the presently claimed methods and administer a compound by any disclosed route of administration of a compound without undue burden.

Further, leptin and variants thereof are well-known in the art. See for example U.S. Patent 6,734,160, which discloses methods of treating diabetes mellitus with OB polypeptide, including fragments, variants and analogs; U.S. Patents 6,429,290 and 6,471,956, which disclose Ob polypeptides, modified forms and compositions thereto, and describes active fragments of the leptin gene; and U.S. Patents 6,350,730 and 6,309,853, which describe leptin polypeptide and polynucleotides, respectively, and fragments and analogs as modulators of body weight. U.S.

Patents 6,350,730 and 6,309,853 are cited as documents A9 and A10 on Applicant's IDS. Copies of U.S. Patents 6,734,160 and 6,471,956 (a CIP of 6,429,290) are submitted herewith (Exhibit A).

In addition to the above cited descriptions of leptin fragments, variants and analogs, the specification describes methods for making leptin variants for administration to a subject, specifically describing which amino acid residues may be changed (page 10, line 1, to page 12, line 8). The specification also describes a method for making a leptin consensus protein using the protein sequence of leptin homologs, and again specifically describes which amino acids may be changed (page 11, lines 1-16). The specification teaches one of ordinary skill in the art how to make a leptin variant and methods for measuring its transport across the blood-brain barrier (see Example 1). As such, a worker of skill in the art could make and use the invention as taught by the Applicant without undue burden.

The Examiner asserts that claims 3 and 4 lack enablement because it is unclear which leptin is being used in the working examples and claims 3 and 4, as amended, are drawn to human leptin, which the Examiner contends may or may not have been used in the Examples. A worker of ordinary skill in the art could readily take a leptin of any species and determine if the leptin is transported across the blood brain barrier without undue burden. Thus, while the claim may be drawn to human leptin, one of ordinary skill would not encounter undue experimentation in determining if the human leptin were as effective as mouse or rat leptin, or vice versa.

The Examiner further contends that the claims are assertedly drawn to non-functional embodiments, such as leptin derivatives or fragments that may not be able to cross the blood-brain barrier. Applicant submits that amendment to claim 3 to recite that the leptin retains the

biological activity of native leptin as well as the ability to cross the BBB obviates this rejection and places a functional limitation on the leptin fragments, analogs, and variants.

The Examiner also contends that the claims, drawn to modulation of leptin transport, are not enabled because Applicant only demonstrates one instance wherein leptin transport is decreased rather than increased. Applicant submits that modulation is enabled because Applicant does show one instance of decreasing leptin transport. As stated above, Applicant is not required to prove every compound is enabled (Atlas Powder Co. *supra*). The Examiner's reliance on working examples in every instance is misplaced. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F2d 904, 164 USPQ 642 (CCPA 1970). Applicant has provided at least one instance of increased leptin transport and decreased leptin transport, supporting the claim of modulating leptin transport.

Because Applicant has taught a worker of ordinary skill in the art to make and use the claimed methods of modulating the transport of leptin across the BBB, by any route of administration, in conjunction with leptin or a leptin fragment analog or consensus sequence, with only routine experimentation, the rejection under 35 U.S.C. § 112, first paragraph, enablement, should be withdrawn.

B. The Rejection of Claims 1-5 Under 35 U.S.C. §112, First Paragraph, Written Description Should Properly Be Withdrawn

The Examiner contends that claims 1-5 lack written description because Applicant has assertedly not described all the compounds recited in the claims, or all leptin variants and fragments encompassed by the claims. Applicant respectfully disagrees.

As indicated by the Examiner, the specification sets out examples of each class of compounds recited in the claims (see page 5, line 3 to page 6, line 9). The specification sets out a representative list and not an exhaustive list of those classes of compounds contemplated by the invention that are numerous, such as neurotransmitters and cytokines In the case of cytokines, the specification sets out exemplary cytokines specifically contemplated by the invention without needing to recite all members of the cytokine family. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. MPEP 213 citing Hybridtech v Monoclonal Antibodies, Inc., 802 F2d 1367, 231 USPQ 81 (Fed Cir. 1986). A worker of ordinary skill can readily review the literature to easily find a list of compounds falling within the classes recited in the claims. The fact that some of the disclosed compounds work or do not work has no relevance to a written description requirement, and is addressed in section II.A above.

As stated previously, biologically active leptin fragments, variants, consensus sequences and the like are well know in the art (See U.S. Patents 6,350,730, 6,309,853, 6,734,160, 6,429,290 and 6,471,956). Moreover, the specification describes how to make leptin fragments, variants, consensus sequences and the like (page 10, line 1, to page 12, line 8). The specification recites which sequences may be made into a leptin fragment polypeptide, which sequences can be changed in the consensus sequence, and to which amino acids they can be changed. The specification also describes that the leptin may have 83% or more identity to the leptin sequences in the claim (page 12, lines 1-2). Given the description provided, a worker of ordinary skill in the art could make the leptin fragments, analogs or variants contemplated by Applicant for use in the invention. One of ordinary skill in the art would also recognize that Applicant was in possession of the invention at the time of filing, given the extensive description

of how to make a leptin fragment, variant or consensus sequence, and which amino acid residues to alter.

As such, the rejection of claims 1-5 under 35 USC §112, first paragraph, written description, should be withdrawn.

C. The Rejection of Claims 1, 2, and 5 Under 35 U.S.C. §102(b), Should Properly Be Withdrawn

The Examiner rejected claims 1, 2, and 5 as assertedly anticipated by the disclosure of Gamaro, which discloses administration of epinephrine to improve memory processes. Gamaro does not address the transport of leptin across the blood brain barrier in response to epinephrine. Further, Gamaro demonstrates that epinephrine administered a dose of 25 μg/kg is effective while a dose of 625 μg/kg impaired memory retention (see Gamaro, abstract).

The present claims, as amended, are directed to methods of modulating transport of leptin by administering an agent in an amount effective to transport leptin across the BBB. As the Examiner notes, the specification demonstrates that a range of epinephrine doses are effective in enhancing leptin transport, from 13.3-66 μg epinephrine/17-22 g mouse, resulting in a range of 605-3882 μg/kg.

For a reference to anticipate, each and every element of the claim must be included in a single reference, and the elements must be arranged as required by the claim. MPEP 2131. Gamaro does not comprise all of the claimed elements. Gamaro makes no reference to the ability of epinephrine to enhance leptin transport, which is required by the claim. Moreover, Gamaro states that a dose in the range Applicant has found effective for the presently claimed invention is not effective for enhancing memory, accordingly teaching away from the presently

claimed invention. As such, the rejection of claims 1, 2, and 5 under 35 U.S.C. §102(b) over Gamaro should be withdrawn.

D. The Rejection of Claims 1, 2 and 5 Under 35 U.S.C. §102(a), Should Properly Be Withdrawn

The Examiner rejected claims 1, 2, and 5 under 35 USC 102(a) as assertedly anticipated by the disclosure of Mostyn, which assertedly teaches administration of adrenaline, a synonym for epinephrine, to mice at a dose of 1000 μg/kg.

While Applicant does not acquiesce to the Examiner's rejection under 35 USC §102(a), the claims have been amended to positively recite administration of epinephrine in conjunction with administration of exogenous leptin. Mostyn discloses only administration of adrenaline alone and provides no testing of co-administration of exogenous leptin and an agent that will facilitate the uptake of leptin across the BBB. Therefore, Mostyn does not anticipate the present claims. As such, the rejection under 35 USC §102(a) should be withdrawn.

E. The Rejection of Claims 1-5 Under 35 U.S.C. §103(a), Should Properly Be Withdrawn

The Examine rejected claims 1-5 under 35 U.S.C. §103(a) as assertedly obvious in view of the disclosure of Gamaro, further in view of Bigsby, further in view of Banks.

Gamaro, discussed previously, assertedly teaches administration of epinephrine in a dose effective for leptin transport. Gamaro neither discloses nor suggest use of epinephrine to enhance leptin transport. Bigsby assertedly discloses that sympathomimetic drugs, including epinephrine, curb appetite. Bigsby neither discloses nor suggests administration of leptin could curb appetite, as the leptin gene was not known at the time of Bigsby. Banks teaches administration of leptin to a mammal to suppress food intake. The Examiner purports that

because leptin and epinephrine assertedly have the same effect, it would be obvious to combine these compounds to curb appetite. Applicant respectfully disagrees.

The art is replete with references that demonstrate that epinephrine appears to decreases mRNA levels of the *ob* gene, thereby decreasing leptin protein levels. See e.g., Mostyn et al. cited by Examiner, Fritsche et al., "Evidence for inhibition of leptin secretion by catecholamines in man" *Exp Clin Endocrinol Diabetes*. 1998, 106:415-8; Carulli et al., "Regulation of ob gene expression: evidence for epinephrine-induced suppression in human obesity" *J Clin Endocrinol Metab*. 1999, 84:3309-12; Bottner et al., "Increased body fat mass and suppression of circulating leptin levels in response to hypersecretion of epinephrine in phenylethanolamine-N-methyltransferase (PNMT)-overexpressing mice" *Endocrinology* 2000, 141:4239-46 (Cited art submitted herewith as Exhibit B). Increased leptin levels into the brain are suggested to be the facilitator of suppressed appetite, thus, a worker of skill in the art would prefer to increase rather than decrease leptin levels. Therefore, at the time of filing, it would have been counterintuitive to administer epinephrine to transport leptin across the blood-brain barrier, and would not be obvious to one of ordinary skill to administer epinephrine in conjunction with leptin to increase leptin levels when epinephrine was believed to decrease leptin levels.

Thus, given the state of the art, a worker of ordinary skill in the art reading Gamaro or Bigsby, which disclose epinephrine, would have no motivation to look to the disclosure of Banks, which discloses administration of leptin, to arrive at the present invention.

Because neither Gamaro nor Bigsby disclose or suggest administration of epinephrine to modulate leptin transport, and neither provide motivation to look to a reference that does refer

to administration of leptin to an individual, the combination of Gamaro, Bigsby and Banks do not render claims 1-5 obvious, and the rejection under 35 USC §103 should be withdrawn.

III. Conclusion

No fees are believed due in connection with the filing of this response, however, should any fees be deemed necessary, the Commissioner is hereby authorized to deduct any such fees from Marshall, Gerstein and Borun LLP account number 13-2855.

Applicants submit that the application is now in condition for allowance and respectfully request notice of the same.

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Respectfully submitted,

By _____

Katherine L. Neville, Ph.D.
Registration No.: 53,379
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Driver, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Agent for Applicants